UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trad mark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/616,371	03/15/96	STAMLER J	DUK96-03

HM11/0605

DAVID E BROOK
HAMILTON BROOK SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON MA 02173-4799

EXAMINER	
CELSA,B	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 06/05/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File
Copy

Office Action Summary	Application No. 08/616,371	Applicant(s) Stamler, J.S.
	Examiner Bennett Celsa	Group Art Unit 1654

☒ Responsive to communication(s) filed on *2/23/98 and 3/16/98* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *4, 5, and 9-29* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *4, 5, 9-14, 28, and 29* is/are allowed.

☒ Claim(s) *15-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Claims 4-5 and 9-29 are currently pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Applicant's amendment and arguments have overcome the indefinite rejection of claims with respect to items A-I and K. With respect to item "A." directed to the indefiniteness of the terms "low molecular weight thiol" and "low molecular weight nitrosothiol" the Examiner notes that applicant described techniques for evaluating molecular weight (e.g. dialysis) and size (e.g. via selective precipitation) of proteins. Additionally, the specification on page 8, lines 21-32 provides a means for comparison of "low molecular weight nitrosothiols" (thiol amino acids) with high molecular weight thiols such as thioproteins (e.g. S-nitrosohemoglobin). Accordingly, the above combined with applicant's discussion rendered the relative term "low" definite.

OUTSTANDING REJECTION(S)

I Claims 15-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

J. Method claims 15-27 are indefinite as to the mode of administration and the administrative amounts.

Discussion

Applicant's arguments directed to the above indefinite rejection of claims 15-27 was considered but deemed partially persuasive for the following reasons. Applicant points to the specification which generally describes modes of administration and doses for human which can be extrapolated from animal data. Although applicant is correct, insofar that the term "administering" would encompass those modalities disclosed or suggested by the specification, the method claims, nevertheless fail to indicate that a particular amount is to be administered. The above rejection is easily overcome by amending the claims to recite "an effective amount". Accordingly, this rejection is hereby maintained.

ii. Claim 15 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Stamler et al. discloses the therapeutic use of "low molecular weight" thiols, S-nitroso-protein and amino acid compounds (e.g. S-nitroso-hemoglobin or myoglobin) for regulating protein function, cellular metabolism including effecting vasodilation;increasing blood oxygen transport by hemoglobin and myoglobin; NO delivery; *in vitro* nitrosylation of molecules present in the body (e.g. see Abstract; pages 1-3 and claims). Stamler discloses a thionitrosylated hemoglobin composition (e.g. see page 58 and claims 13-16) comprising reacting hemoglobin in the presence of oxygen with a nitrosating agent (e.g. SNOAc) which composition anticipates that presently claimed. If equimolar amounts of nitrosating agent and Hb constitute "excess nitrosating agent" than the reference method anticipates the presently claimed method. Alternatively optimizing nitrosylating amounts to achieve "excess" nitrosation of hemoglobin to insure nitrosylation of hemoglobin would be obvious to the skilled artisan at the time of applicant's invention. The reference method of forming thionitrosylated oxygenated hemoglobin would either immediately envisage (e.g. anticipate) or alternatively render obvious the formation of thionitrosylate deoxygenated hemoglobin under anaerobic conditions as presently claimed. The reference specifically discloses the use of nitrosylated proteins (e.g. S-nitroso hemoglobin) and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport;

modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims). The combination of nitrosating agents (e.g. thionitrosylated "Low" molecular weight and "high" molecular weight compounds; e.g. nitrosothiol, glutathione and hemoglobin) would be prima facie obvious to the skilled artisan at the time of applicant's invention in order obtain the increased pharmaceutical effects of the agents.

iii. Claims 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier), Klatz et al., U.S. Pat. No. 5,395,314 (3/95: file 6/93 or earlier) and Hunter, U.S. Pat. No. 5,152,979 (10/92).

The discussion of the teaching of the Stamler et al. reference in the above rejection under 35 USC102/103 is hereby incorporated by reference in its entirety. To summarize, the Stamler et al .reference discloses the use of S-nitrosating agents (e.g. low molecular weight e.g. glutathione and hemoglobin derivatives) to treat disorders by achieving a variety of physiological effects including vasodilation; radical scavenging ; NO and oxygen delivery. The above reference does not explicitly disclose the use of nitrosating agent(s) to preserve living organs, treat malaria or sickle cell anemia. Feola et al. disclose the use of "blood substitutes" to restore blood volume, transport oxygen and reduce vasoconstriction (e.g. vasodilate) by the use of hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7). Hunter discloses that malaria is a blood disorder which results in ischemia caused by compromised microvasculature (e.g. see abstract and col. 1). Klatz et al. disclose a brain resuscitation and organ preservation composition which comprises perfluorocarbons which act as "a blood substitute" which "transport(s) oxygen in a manner similar to hemoglobin" (e.g. see Abstract, col. 1, col. 4, lines 1-25). The Stamler et al. reference provides the skilled artisan with motivation to use nitrosating agents alone or combined to treat disorders of diseases to which vasodilation and oxygen/NO transport would prove to be therapeutic. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize thionitrosating agents (e.g. hemoglobin, glutathione) as blood substitutes to treat blood disorders such as sickle cell anemia or malaria since the Feola reference discloses the use of hemoglobin and thiol containing blood substitutes to treat anoxic blood disorders (e.g. sickle cell anemia as disclosed by Feola and malaria as disclosed by Hunter) and Stamler provides a reasonable expectation that nitrosating agents will be successful to achieve the desired effects of blood substitutes. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize nitrosating agents for organ preservation since the Katz reference provides motivation to utilize compositions such as perfluorocarbons for their ability to act as "blood substitutes" and hemoglobin oxygen transporters and Stamler teaches that nitrosating agents would be successful to achieve the desired effects of blood substitutes and also act as effective hemoglobin oxygen transporters.

Discussion

Applicant's arguments and submitted 132 Declarations directed to the anticipation (e.g. 102/103) and obviousness rejections presented above have been considered and been deemed partially persuasive with regard to all the claims, with the exception of claim 15. The 35 USC 132 Declaration of Dr. Stamler and Dr. Bonaventura were review by the Examiner and found persuasive toward establishing the nonenablement of the WO 93/09806 in making SNO-hemoglobin. However, claim 15 encompassed a method of delivering oxygen by administering a low molecular weight thiol or nitrosothiol and hemoglobin **OR S-nitrosohemoglobin**. The Stamler reference alone (e.g. see pages 1-3 and abstract) or when combined with Feola and/or Katz clearly disclose the presently claimed method of delivering oxygen by using a combination of a low molecular weight thiol or nitrosothiol and hemoglobin. The prior art rejection of claim 15 will be withdrawn by amending this claim to require the presence of **S-nitrosohemoglobin**. Accordingly, this rejection is hereby retained.

Allowable Subject Matter

3. Claims 4-5 and 9-14 and 28-29 are allowable over the prior art of record.

4. Claims 16-27 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June 4, 1998

B.C.

C Tsang

CECILIA J. TSANG
SUPERVISORY PATENT EXAMINER
GROUP 1800